REMARKS

Status of the Claims and Amendment

Claims 1 and 18 are amended herein to refer to one or plural reagents selected from the group consisting of formalin, paraformaldehyde and trioxane. In view of the amendment to claim 18, claim 19 is amended to refer to "the reagent". Support for these amendments is found, for example, at page 7, the 7th paragraph.

Claim 9 is amended herein by further defining variables R^3, R^{11}, R^{12}, R^{14}, R^{15}, R^{16}, R^{23}, R^{24}, R^{25} and R^{26}. Support for the amendment is found, for example, at page 7, paragraphs 1-5.

Claims 37-52 are canceled herein.

No new matter is presented.

Upon entry of the amendment, claims 1-3, 7-36 and 53-57 will be all of the claims pending in the application.

Response to Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

On page 2 of the Office Action, the Examiner rejects Claims 1-3, 7 and 8 under 35 U.S.C. 112, second paragraph, as allegedly being indefinite.

The Examiner contends that use of the phrase "synthon of formaldehyde" in Claim 1 does not have a definite meaning that would allow one of ordinary skill in the art to recognize the metes and bounds of the claim. The Examiner acknowledges that Claim 1 recites "at least one selected from the group consisting of ...," however, this is construed by the Examiner to provide examples of exemplary species, rather than further define what the "synthon" is limited to.

Applicants respectfully disagree with the Examiner's position that the language used in Claim 1 could be construed as providing examples of exemplary species, without actually further limiting what the "synthon of formaldehyde". Notwithstanding the above, without conceding the merits of the rejection, claim 1 is amended herein to recite that the step 1 of the reaction is conducted in the presence of one or plural reagents selected from the group consisting of formalin, paraformaldehyde and trioxane as supported by the specification at page 7, paragraph 7. When properly read in light of the specification, one of ordinary skill in the art would readily be able to understand the metes and bounds of the claim.

Accordingly, Applicants respectfully request withdrawal of the §112, 2nd paragraph, rejection.

Response to Claim Rejections Under 35 U.S.C. § 103(a)

The Examiner does not appear to have set forth any additional grounds upon which the obviousness rejection is based. Rather, the Examiner appears to have only provided comments on Applicants' rebuttal arguments presented in the Amendment filed October 29, 2007 in response to the Action dated May 29, 2007.

With regard to newly introduced Claims 53-57, the Examiner states that these claims are rejected under 35 U.S.C. 103(a) as being obvious over Shiota *et al.* in view of Katritzky *et al.* for those same reasons Claims 1-3 and 7-52 were rejected. The Examiner alleges that the methods of Katritzky *et al.* are within the contemplation of one of ordinary skill in the art for use with Shiota *et al.* because Katritzky *et al.* disclose methods of producing indole derivatives, which the Examiner alleges is what the instant application attempts.

With regard to Claims 15 and 16, the Examiner states that the rejection is maintained because one of ordinary skill in the art allegedly would immediately recognize that protecting group chemistry is appropriate when forming a peptide bond. Further, the Examiner contends that Schelhaas *et al.* disclose the optimal choice of protecting groups in complex multistep synthesis involving the formation of a peptide bond.

With regard to Claims 17-20, 24-31 and 45-52, the Examiner maintains his position that the potential motivation to modify the synthetic scheme taught by Shiota *et al.* so as to begin with simpler, readily available starting materials, is valid. The Examiner further opines that one of ordinary skill in the art of organic synthesis is motivated to optimize yields of reactions to obtain the most product possible in a single reaction, such as by reformulating reactions using well known synthetic routes.

With regard to Claims 21-23, the Examiner has found Applicant's arguments unpersuasive, asserting that use of a palladium catalyst for removing protecting groups as disclosed in Schelhass *et al.* "is well known in the art and one of ordinary skill in the art would know to apply it [to a benzyl group]."

In view of the above, the Examiner asserts that Claims 1-3 and 7-57 are obvious over the prior art and are properly rejected under 35 U.S.C. § 103(a).

Applicants respectfully traverse the rejection.

With respect to claims 1-3, 7, 8 and 32-26, the Examiner has failed to rebut Applicants' previous arguments. Specifically, in the rejection of Claims 1-8 under 35 U.S.C. § 103(a) set forth in the Office Action mailed May 29, 2007, the Examiner alleges that "Shiota *et al.* teaches

several specific products and methods of making including species which anticipate the genus of the instantly claimed methods," which is assumed to be the compounds set forth in the rejection under 35 U.S.C. § 102(b) over Shiota *et al.* In the current Office Action, all the anticipation rejections have been withdrawn.

Although the Examiner appears to believe that Shiota *et al.* renders obvious the reaction steps of Claim 1, the Examiner has not set forth any reasons to support his position. The Examiner clearly admits that Shiota *et al.* does not anticipate the currently claimed invention because the section 102 rejections have been withdrawn, but no reasons are provided as to why Shiota *et al.* renders the method of Claim 1 obvious.

Further the production method disclosed by Shiota *et al.* does not teach or suggest the production method of Claim 1, that is, a reaction scheme that utilizes an indole derivative which is not substituted at the 3-position.

Further still, Shiota *et al.* does not teach or suggest the subject matter of Claim 1. The preparation processes 2 and 3 of Shiota *et al.* only suggest reaction by indolyl-CH_2-X and reaction by indolyl-CHO, respectively. Shiota *et al.* does not suggest a reaction by indolyl-H of the present invention. For example, the reaction mechanism of Shiota *et al.* (i.e., "preparation process 3") utilizes an indole derivative substituted with an alkyl group and an aldehyde group at the 3-position. Thus, Shiota *et al.* is distinct from the claimed method, which requires an indole derivative without a substituent at the 3-position, and also the addition of one or plural reagents selected from the group consisting of formalin, paraformaldehyde and trioxane. The Examiner has not explained why Shiota *et al.* teaches or suggests the reaction step wherein the indole

derivative does not have a substituent at the 3-position, and wherein the condensation reaction uses formalin, paraformaldehyde and trioxane.

Given the mechanistic differences between the two reactions, Applicants submit that Shiota *et al.* can not reasonably be applied to support a finding of obviousness of Claim 1.

2. With regard to Claims 9-31, on page 4 of the Office Action the Examiner appears to maintain that these claims "are using well-known methods in peptide chemistry and therefore remain obvious."

Applicants respectfully traverse the rejection.

Applicants note that the Examiner has withdrawn the section 102 rejections over Shiota *et al.*, thus the Examiner admits that Shiota *et al.* does not disclose a condensation step using an anthranilic acid derivative in a mixed solvent of aprotic solvent and C_{1-3} alcohol. The Examiner appears to assert that this would be obvious, however, Applicants disagree. Specifically, Shiota *et al.* do not disclose or even suggest using an anthranilic acid derivative in a mixed solvent of aprotic solvent and C_{1-3} alcohol, and none of the secondary references cited by the Examiner compensates for this deficiency. Thus, even if the references were combined the present invention would not have been achieved since the cited references fail to teach each and every element of the claims, as is required to support an obviousness rejection. For at least this reason the present invention is not rendered obvious by the cited references.

Further, although the Examiner has acknowledged consideration of the Rule 132 Declaration, the Examiner has not set forth any reasons why the unexpectedly superior properties of the reaction when using an anthranilic acid derivative in a mixed solvent of aprotic solvent

and C_{1-3} alcohol are not persuasive, particularly in view of the fact that none of the cited references disclose use of such a mixture.

Specifically, neither reference, either alone or in combination, discloses or even suggests using an anthranilic acid derivative in a mixed solvent of aprotic solvent and C_{1-3} alcohol for a condensation step. Without conceding the merits of the rejection, the claims are amended herein to recite that R^3, R^{11}, R^{12}, R^{14}, R^{15}, R^{23}, R^{24} and R^{26} are each hydrogen; R^{16} is hydrogen or a methyl group; and R^{25} is a trifluoromethoxy group as supported by the present specification at page 7, paragraphs 1-5. As evidenced by the Declaration, the claimed mixture clearly possesses unexpectedly superior properties with regard to solubility of the claimed compound on an industrial scale, which is unappreciated by the prior art. For this additional reason the present invention is patentable over the cited references whether taken alone or in combination.

3. With regard to Claims 53-57, the Examiner asserts that these claims are obvious over Shiota *et al.* in view of Katritzky *et al.*, as set forth in the 35 U.S.C. § 103(a) rejection in the Office Action mailed May 29, 2007. Applicants note that in the Office Action mailed May 29, 2007, the previous rejection was based on Shiota *et al.*, Katritzky *et al.* and Schelhaas *et al.* It is not clear whether the Examiner intended to include Schelhaas *et al.* in the present rejection since the at page 3, the Action states that claims 53-57 are rejected as being obvious over Shiota *et al.* and Katritzky *et al.*, but Schelhaas *et al.* is mentioned at page 4 of the Action.

Regardless, Applicants respectfully traverse the rejection and submit that one of ordinary skill in the art would not have been motivated to combine the references as suggested by the Examiner. Specifically, Shiota *et al.*, Katritzky *et al.* and/or Schelhaas *et al.* do not teach or

suggest the methods of Claims 53-57 because one of ordinary skill in the art would have no reason to choose a dialkylaminomethyl group as a protecting group on the indole derivative.

The Examiner admits that Shiota *et al.* does not specifically select a dialkylaminomethyl protecting group on the indole. The Examiner also admits that Shiota *et al.* does not teach the specific reaction of the amine deprotection step described in reaction step 4 as recited in claims 15 and 16.

Katritzky *et al.* does not remedy the deficiencies of Shiota *et al.*

There are two differences between Katritzky *et al.* and the present invention.

First, in Katritzky *et al.*, a dimethylaminomethyl group is utilized as a protecting group and therefore it would be completely removed after the intended key step is perfected in Katritzky *et al.* On the other hand, in the present invention, the dimethylaminomethyl group is used to introduce an indolylmethyl group to the pyrrole nitrogen and therefore the dimethylaminomethyl group is not completely removed after the reaction. Instead the methylene portion remains to form a bridge between the pyrrole nitrogen and the indolyl group in the present invention. Katritzky *et al.* is silent about the use of dimethylaminomethyl group on an indolyl group in such a manner.

Secondly, the dimethylaminomethyl group is introduced to nitrogen atom of indole ring in Katritzky *et al.*, whereas in the present invention it is introduced to the 3-position carbon atom on the indole ring in the present invention, which was not suggested by Katritzky *et al.*

Accordingly, there is no reason or motivation for one of ordinary skill in the art to modify the method of Shiota *et al.* with the teachings of Katritzky *et al.* with a reasonable expectation of obtaining the claimed method.

Schelhaas *et al.* is also silent about the use of dimethylaminomethyl group on an indolyl group in the manner described above for the present invention and fails to remedy the deficiencies of Shiota *et al.* and Katritzky *et al.*

Accordingly, the present invention is not rendered obvious by the cited references, whether taken alone or in combination.

4. Claims 37-52 are canceled herein, thereby rendering the rejection moot as to these claims.

In view of the above, Applicants respectfully request withdrawal of the §103 rejections.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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